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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,839	03/04/2005	Frederic Becq	50376/003001	4276

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EXAMINER	
AULAKH, CHARANJIT	
ART UNIT	**PAPER NUMBER**
1625	

NOTIFICATION DATE	DELIVERY MODE
01/08/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/516,839	BECQ ET AL.	
	Examiner	Art Unit	
	Charanjit S. Aulakh	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *12 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,14-16,18-20 and 22* is/are rejected.

7)☒ Claim(s) *17 and 21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/3/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. According to paper filed on Nov. 27, 2007, the applicants have elected group I with traverse in response to restriction requirement.

2. Claims 1-22 are pending in the application. Claims 12 and 13 are withdrawn from further consideration as being directed to non-elected group.

Response to Arguments

3. Applicant's arguments filed on Nov. 27, 2007 have been fully considered but they are not persuasive regarding restriction requirement. The examiner does not agree with the applicant's arguments on page 2 that all the three groups directed to tricyclic ring structure, tetracyclic ring structure and pentacyclic ring structure have common core. As stated clearly in the last office action, each of these three groups have a separate core. Also, according to compounds disclosed in the specification are directed to only one of these three groups and therefore, there is no reason for any additional groups. Thus, restriction requirement as indicated is proper and thereby made final.

Information Disclosure Statement

4. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a

separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

5. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

6. In regard to brief description of drawings, the applicants mention " Legend to figures " on page 30. The applicants are suggested to change this term with " Brief description of drawings " which is generally used.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The following eight different factors (see Ex parte Foreman, 230 USPQ at 547; Wands, In re, 858.F. 2d 731, 8 USPQ 2d 1400, Fed. Cir. 1988) must be considered in order for the specification to be enabling for what is being claimed:

Quantity of experimentation necessary, the amount of direction or guidance provided, presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability and the

breadth of claims. In the instant case, the specification is not enabling based on atleast four of the above mentioned eight different factors such as quantity of experimentation necessary, the amount of direction or guidance provided, presence of working examples, state of the prior art, unpredictability and the breadth of claims.

In regard to lack of enablement issue of instant claims 1-11 for derivatives (such as hydrates, solvates or prodrug forms) of instant compounds of formula (I), there is no teaching or guidance present in the specification for preparing any specific hydrates (mono, di, tri or tetra), solvates or prodrugs. Preparation of specific hydrates or solvates of any compound is a very specialized field and involves their characterization using different techniques such as infrared spectrum, XRD powder diffraction etc. There is no teaching or guidance present in the specification regarding any specific solvents used for preparing specific hydrates or solvates and their characterization using any techniques such as XRD powder diffraction or infrared spectrum etc. There is not even a single example present for preparing any specific hydrate or solvate of instant compounds of formula (I). There is lot of unpredictability regarding stability of different hydrates or solvates of any compound in the art. The instant compounds of formula (I) encompasses hundreds of thousands of compounds based on the values of variables R1-R%, R7-R10, Y and A and therefore, in absence of such teachings, guidance, presence of working examples and unpredictability, it would require undue experimentation to select specific hydrates or solvates of instant compounds with enhanced stability properties.

In regard to prodrug forms, there is no teaching or guidance present in the specification for preparing specific types of prodrug form such carboxylic acid esters, amino acid or amide esters, phosphate esters, phosphono esters , sulfate esters etc. There is not even a single working example present in the specification for preparing any type of specific prodrug form of instant compounds of formula I. There is lot of unpredictability in the art for efficacy of different types of prodrug forms of any known compound following their in vivo administration since their efficacy depends upon various factors such as absorption from gut, metabolism by esterases etc. The instant compounds of formula (I) encompasses hundreds of thousands of compounds based on the values of variables R1-R5, R7-R10, Y and A and therefore, in absence of such teachings, guidance, presence of working examples and unpredictability, it would require undue experimentation to select specific types of prodrug forms of instant compounds of formula (I) which will be effective following in vivo administration.

In regard to enablement rejection of claims 1-11 for methods of treatment, the specification teaches that the instant compounds are activators of CFTR channel. There is no teaching or guidance present in the specification or prior art that hypoactivity of CFTR channel is implicated in the etiology of every known vascular disorder or respiratory disorder. There is no teaching in the prior art that structurally closely related compounds having CFTR channel activating activity are well known to have therapeutic utility in treating every known vascular disorder or respiratory disorder including arterial hypertension and asthma. There are no working examples present showing efficacy of instant compounds in known animal models of every known vascular disorder or

respiratory disorder including arterial hypertension and asthma. The instant compounds of formula (I) encompasses hundreds of thousands of compounds based on the values of variables R1-R5, R7-R10, A and Y and therefore, in absence of such teachings, guidance, presence of working examples and prior art, it would require undue experimentation to demonstrate efficacy of instant compounds in known animal models of every known vascular disorder and respiratory disorder and hence their utility for treating these disorders.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-11, 14-16, 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim1, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to

whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 1-3, 5, 7, 9, 14-16, 18 and 19 recite the broad recitation halogen for the values of variables X, R1-R5 and R7-R10, and the claim also recites chlorine, bromine or fluorine which is the narrower statement of the range/limitation. Similarly, claims 2, 3, 5, 7, 9, 14-16 and 19 recite the broad recitation alkyl for the values of variables R' or R5, and the claim also recites ethyl or butyl which is the narrower statement of the range/limitation.

Claims 2-4, 7, 8 and 15 recites the limitation "-SH or –NHCOCH3 for variable Y" in claim 1 or 14. There is insufficient antecedent basis for this limitation in the claim.

Claims 1-11 provides for the use of derivatives of formula (I), but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

11. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

12. Claims 1-11 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Becq (WO 98/05642, cited on applicant's form 1449).

Becq discloses CFTR channel activator compounds, pharmaceutical compositions containing these compounds and their use for treating cystic fibrosis. The pharmaceutical compositions containing compounds disclosed on pages 14-21 by Becq anticipate the instant claims when R5 represents variables other than an ester in the instant compounds of formula (I).

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. Claims 18-20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becq (U.S. Patent 6,630,482).

Becq discloses CFTR channel activator compounds, pharmaceutical compositions containing these compounds and their use for treating cystic fibrosis. The compounds of formula (III) disclosed in column 10, lines 1-17 as well as compounds 12, 18-21 and 25-27 (see columns 11-13) disclosed by Becq meet all the limitations of instant claims except that variable Y represents SH group in the instant claims instead of an OH group. However, both oxygen and sulphur atoms belong to the same class of chalcogens. Therefore, it would have been obvious to one skilled in the art to prepare the instant compounds substituted with SH group at 6^{th} position instead of an OH group without affecting their utility of activating CFTR channels with reasonable expectation of success.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 1-11, 18-20 and 22 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,630,482. Although the conflicting claims are not identical, they are not patentably distinct from each other because the pharmaceutical composition for activating CFTR channels containing compounds of claim 1 of the cited patent anticipate the instant claims 1-11 when instant variable R5 is either H or other than an ester and furthermore, it would

have been obvious to one skilled in the art to prepare the instant compounds of claims 18-20 and 22 substituted with SH group at 6th position instead of an OH group without affecting their utility of activating CFTR channels with reasonable expectation of success since both oxygen and sulphur atoms are chalcogens.

19. Claims 1-5, 7, 14-16, 18, 19, 21 and 22 are objected for containing non-elected subject matter.

Allowable Subject Matter

20. Claims 17 and 21 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charanjit S. Aulakh whose telephone number is (571)272-0678. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

C. S. Aulakh

Charanjit S. Aulakh
Primary Examiner
Art Unit 1625